CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85035

APPROVAL LETTER

7/5/77

NDA 85-035

Generic Pharmaceutical Corp.
Attention: Mr. Bernard Abramson
433 Commercial Avenue
Palisades Park, NJ 07650

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diphenoxylate HCl & Atropine Sulfate Tablets, (2.5 mg. & 0.025 mg. respectively).

We acknowledge receipt of your communication dated May 27, 1977, amending the application.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application, requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

Promotion of a product marketed under an abbreviated new drug application must not convey the impression that the product is a new entity.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

/S/

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

7/5/77

NDA Dup JMeyer 7/1/77
HFD-614 HFD-616
VVKarusaitis/JMeyer/GMillar 6-29-77
rd/ init. JMeyer/MSeife 6-30-77
f/t/wlb/6-30-77
approved. 7/1/77

MVK/MS 7/1/77

Enclosures:
Conditions of Approval of a New Drug Application
Records and Reports Requirements

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85035

DRAFT FINAL PRINTED LABELING

REV: 9/76

DIPHENOXYLATE TABLETS U.S.P
(with Atropine Sulfate)

DESCRIPTION: Each Diphenoxylate tablet contains:

Diphenoxylate HCl U.S.P. ..... 2.5 mg.
(Warning: May be habit-forming)
Atropine Sulfate U.S.P. ..... 0.025 mg.

IMPORTANT INFORMATION: Diphenoxylate is classified as a Schedule V substance by federal law; however, it is chemically related to the narcotic meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine intoxication, in which prolonged and careful monitoring is essential, since respiratory depression may be evidenced as late as 30 hours after ingestion and may recur in spite of an initial response to Narcan® (naloxone hydrochloride). DIPHENOXYLATE HYDROCHLORIDE IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.

ACTIONS: Diphenoxylate acts by slowing intestinal motility.

INDICATIONS: Diphenoxylate is effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS: Diphenoxylate is contraindicated in children less than 2 years of age due to the decreased margin of safety in younger age groups. It is also contraindicated in patients with a known hypersensitivity to diphenoxylate hydrochloride or atropine and in patients who are jaundiced.

WARNINGS: Diphenoxylate should be used with special caution in younger children because of the greater variability of response in this age group. Its use does not preclude the administration of appropriate fluid and electrolyte therapy. Dehydration, particularly in younger children, may further influence the variability of response to Diphenoxylate and may predispose to delayed diphenoxylate intoxication. Drug-induced inhibition of peristalsis may result in fluid retention in the colon which may further aggravate dehydration and electrolyte imbalance. If severe dehydration or electrolyte imbalance is manifested, diphenoxylate should be withheld until appropriate corrective therapy has been initiated.

Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of it with monoamine oxidase inhibitors may, in theory, precipitate hypersensitive crisis.

Diphenoxylate should be used with extreme caution in patients with cirrhosis and other advanced hepatic disease and in all patients with abnormal liver function tests, since hepatic coma may be precipitated.

Diphenoxylate hydrochloride may potentiate the action of barbiturates, tranquilizers and alcohol. Therefore, the patient should be closely observed when these medications are used concomitantly.

Usage in pregnancy: The use of any drug during pregnancy, lactation, or in women of child-bearing age requires that the potential benefits of the drug be weighed against any possible hazard to the mother and child. Effects of diphenoxylate hydrochloride or atropine sulfate may be evident in the infants of nursing mothers taking diphenoxylate hydrochloride since these compounds are excreted in breast milk.

PRECAUTIONS: Addiction (dependency) to diphenoxylate hydrochloride is theoretically possible at high dosage. Therefore the recommended dosage should not be exceeded.

Because of the structural and pharmacological similarity of diphenoxylate hydrochloride to drugs with a definite addiction potential, it should be administered with considerable caution to patients who are receiving addicting drugs, to individuals known to be addiction prone, or to those whose histories suggest they may increase the dosage on their own initiative.

In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and diphenoxylate therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Because a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride to discourage deliberate overdosage, there should be strict observance of the contraindications, warnings and precautions for the use of atropine.

In children, Diphenoxylate should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's Syndrome.

ADVERSE REACTIONS: Atropine effects, such as dryness of the skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention may occur, especially in children. Other adverse reactions reported with diphenoxylate use are:

Nausea	Drowsiness (sedation effect)
Sedation	Coma
Vomiting	Lethargy
Swelling of the gums	Anorexia
Abdominal discomfort	Restlessness
Numbness of the extremities	Euphoria
Headache	Pruritus
Dizziness	Angioneurotic edema
Depression	Giant urticaria
Malaise	Paralytic urticaria
Respiratory depression	Toxic megacolon

DOSAGE AND ADMINISTRATION: Adults: The recommended initial dosage is two tablets four times a day. Most patients will require this dosage level until initial control is effected, after which the dosage should be reduced to meet individual requirements; control may often be maintained with as little as 5 mg. (two tablets) daily.

Children: Diphenoxylate is contraindicated in children under 2 years of age. It should be used with special caution in young children due to the variable response in this age group. For children over 2 years of age, the recommended daily dosages expressed in divided doses and according to the child's age are given in the following table:

Children: In children 2 to 12 years of age it is preferable not to use tablets. However, the following schedule is presented as a guide.

Age:	Dosage:
2 to 5 years	2 mg. t.i.d.
5 to 8 years	2 mg. q.i.d.
8 to 12 years	2 mg. 5 times daily

Do not exceed recommended dosage.

Adults: Two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d.

Maintenance dosage may be as low as one fourth of the initial daily dosage. Downward adjustment of dosage should be made as soon as initial control of symptoms is accomplished.

OVERDOSAGE: Diagnosis and Treatment: Caution patients to adhere strictly to recommended dosage schedules. The medication should be kept out of reach of children, since accidental overdosage may result in severe, even fatal, respiratory depression. In the event of overdosage (initial signs may include dryness of the skin and mucous membranes, flushing, hyperthermia and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils and respiratory depression), gastric lavage, establishment of a patent airway and possibly mechanically assisted respiration are advised.

The narcotic antagonist, Narcan® (naloxone hydrochloride) may be used in the treatment of respiratory depression caused by narcotic analgesics or pharmacologically related compounds such as Lomotil. When Narcan is administered intravenously the onset of action is generally apparent within 2 minutes. Narcan may also be administered subcutaneously or intramuscularly providing a slightly less rapid onset of action but a more prolonged effect.

To counteract respiratory depression caused by Lomotil overdosage, the following schedule for Narcan should be followed:

Adult Dosage: The usual initial adult dose of Narcan is 0.4 mg. (one ml.) administered intravenously. If respiratory function does not adequately improve after the initial dose the same I. V. dose may be repeated at two-to-three-minute intervals.

Children: The usual initial dose of Narcan for children is 0.01 mg. per kilogram of body weight administered intravenously and repeated at two-to-three-minute intervals if necessary.

Following the initial improvement of respiratory function, repeat doses of Narcan may be required in response to recurrent respiratory depression. Supplemental intramuscular doses of Narcan may be utilized to produce a longer lasting effect.

Since the duration of action of diphenoxylate hydrochloride is longer than that of naloxone hydrochloride, improvement of respiration following administration may be followed by recurrent respiratory depression. Consequently, continuous observation is necessary until the effect of diphenoxylate hydrochloride on respiration (which effect may persist for many hours) has passed. The period of observation should extend over at least 48 hours, preferably under continuous hospital care.

It should be noted that, although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

HOW SUPPLIED: Tablets—white, containing 2.5 mg. of diphenoxylate hydrochloride and 0.025 mg. atropine sulfate; bottles of 100, 500 and 2,500.

A subtherapeutic amount of atropine sulfate is included to discourage deliberate overdosage.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By

GENERIC PHARMACEUTICAL CORPORATION
Palisades Park, New Jersey 07650

APPROVED
JUL [illegible] 1977

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85035

MEDICAL REVIEW

REVIEW OF RESUBMISSION

DATE COMPLETED: 6-22-77

ANDA #: 85-035

CO. NAME: Generics Pharmaceutical Corp
Palisades Park, NJ 07650

NAME OF DRUG: Diphenoxylate HCl + Atropine Sulfate Tablets
2.5 mg. 0.25 mg.

DATE OF SUBMISSION: 5-27-77

TYPE OF SUBMISSION: RESUBMISSION - reply to FDA letter 2-22-77

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.
Bio requirement - not required.

2. Review of Labeling:

a) Container labels: satisfactory CV
Dipheroxylate 2.5 mg. bottles of 500, 1000
w/Atropine Sulfate

"J-Davis"

b) Insert labeling: Satisfactory (MOR 12-6-75)
date: 9-76

CONCLUSION: labeling is satisfactory

RECOMMENDATIONS: The firm is to be so notified.

/S/
V.V. Karusaitis, M.D.

cc:dup
VVK/wlb/6-22-77

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 85-035

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM: [XX] Bureau of Drugs
[ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

ORIGINAL ABBREVIATED

TYPE OF APPLICATION
[ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [XX] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY
[XX] HUMAN [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG
diphenoxylate HCl + atropine sulphate

DOSAGE FORM: oral

HOW DISPENSED
[XX] RX [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

diphenoxylate HCl +
atropine SO4
2.5/0.025 mgs

NAME OF APPLICANT *(Include City and State)*

Generic Pharmaceutical Corp.
Palisades Park, NJ 07650

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

antiperistaltic

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: apillar — DATE:

FORM APPROVED BY

NAME: jlmeyer — DATE:

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

REVIEW OF AMENDMENT, RESUBMISSION, FPL

DATE COMPLETED: 11-30-76 ANDA #: 85-035

CO. NAME: Generic Pharm. Corp.
Palisades Park, NJ 07650

NAME OF DRUG: Diphenoxylate 0.25 mg. (with atropine sulfate 0.25 mg.) Tablets

DATE OF SUBMISSION: 11-12-76

TYPE OF SUBMISSION: Amendment, FPL

CLINICAL EVALUATION:

Pertinent material is to be reviewed by the chemist. Comparative dissolution study: "Lomotil" versus Generic Product.

1. Review of Labeling:

a) Container labels: Satisfactory CV
2.5 mg. tablets bottles of 500, 1,000

b) Insert labeling: Satisfactory
Date: 9-76

QUESTION: Propriety of Pharmacist warning to Patient???
RECOMMEND: Deletion of reference to pharmacist.

CONCLUSION: Insert labeling is satisfactory for the safe and effective use of this product. Question of propriety of Pharmacist warning to patient.

RECOMMENDATIONS: The firm is to be so notified.

/S/
V.V. Karusaitis, M.D.

cc:
Dup
VVK/wlb/12-6-76

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85035

CHEMISTRY REVIEW(S)

OR SUPPLEMENT

AE Number 85-035

ame and Address of Applicant (City and State)

generic pharmaceutical corp
palisades park, NJ 07650

Original
Amendment
Supplement
Resubmission
Correspondance
Report
Other

urpose of Amendment/Supplement

orig abbr NDA

Date(s) of Submission(s)

11/12/70

harmacological Category	Name of Drug	
antiperistaltic	diphenoxylate HCl + atropine SO4	
osage Form(s)	Potency(ies)	How Dispensed
oral	2.5 + 0.025 mgs respectively	R_x xxx OTC
ackaging/Sterilization	Samples	Related IND/NDA/MF
submitted	requested	

abeling

as per MO(vvkaruaitis)

iologic Availability

NA

stablishment Inspection

requested

omponents, Composition, Manufacturing and Controls

as per letter to issue

emarks

rev w/f gmillar

onclusion

EVIEWER DATE

		AF Number 85-035
Name and Address of Applicant (City and State) generic pharmaceutical corp. palisades park. NJ 07650		Original Amendment Supplement Resubmission Correspondance Report Other
Purpose of Amendment/Supplement amend		Date(s) of Submission(s 5/27/77
Pharmacological Category antiperistaltic	Name of Drug diphenoxylate HCL _ atropine SO4	
Dosage Form(s) oral	Potency(ies) 2.5/0.025 mgs	How Dispensed R_x xxx OTC
Packaging/Sterilization submitted	Samples validated by NY-DO as per5/2/77 review	Related IND/NDA/MF

Labeling

as per MO(vvkarusatis)
containers additionally bear JDAVIS name

Biologic Availability

NC-deferred

Establishment Inspection

in compliance as per HFD-332 memo of 2/15/77

Components, Composition, Manufacturing and Controls

satisfactory
NB: proposed dissolution procedure = extr quality control

Remarks

approved gmillar
April 7/1/77

Conclusion

REVIEWER DATE